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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,078	11/08/2001	Donna T. Ward	RTS-0236	6940

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	4

DATE MAILED: 05/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 10/007,078	Applicant(s) WARD ET AL.	
	Examiner J. Douglas Schultz	Art Unit 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 07 May 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☒ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1, 2, 4-15, 20-24, 26 and 27 stand rejected for the same reasons of record as set forth in the Office action mailed February 7, 2003*.

   Claim(s) withdrawn from consideration: _____.

8. ☒ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 2. NOTE: The proposed amendment contains claim language drawn to the percent-inhibition achieved by the subject nucleic acid inhibitors of the EIF2C1 target gene. Said language pertaining to said % inhibition has not been recited in any claim heretofore, and raises new search and examination issues not previously considered. For example applicants' inclusion of language relating to percent inhibition could potentially raise issues under 35 U.S.C. § 112 1st paragraph regarding the breadth of such percent-inhibition language in relation to the amount of guidance and enabling disclosure provided in the specification. To be sure, these rejections are not being levied herein, but rather are discussed in order to highlight potentially new issues that may arise by the inclusion of said claims.

Continuation of 5. does NOT place the application in condition for allowance because: applicants' arguments are not considered convincing. Applicant argues that the Office mischaracterized the references of Crooke et al ("Crooke")., and Gewirtz et al. ("Gewirtz") by asserting that passages cited to demonstrate lack of enablement do not support the examiner's conclusion. This is not convincing, because applicants' reiteration of the cited passages and subsequent analysis of them are themselves either mischaracterized or taken out of context. For example, applicants argue the a passage from Gewirtz that discusses the use of a transfection agent that works well in vitro needs to be studied more in vivo is not relevant, because applicant is not claiming the use of a transfection agent. However, the passage was cited to underscore how in vitro results do not correlate well with in in vivo results. Applicants response does not address this central point.

In another example, applicants have argued that a passage citing the inappropriateness of using in vitro uptake results to make predictions about in vivo pharmacokinetic behavior has been mischaracterized. To quote the passage from Crooke (pg. 3): "Finally, extrapolations from in vitro uptake studies to predictions about in vivo pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man that demonstrate that, even after careful consideration of all in vitro uptake data, one cannot predict in vivo pharmacokinetics of the compounds based on in vitro studies...". The Office action concluded from this that "According to the reasoning in this passage, it follows that any oligo which is taken up by a cell in vitro, even if it proceeds to inhibit the target, that no meaningful prediction can be made as to whether the oligo will ever be taken up by cells in vivo". Applicants appear to support this line of reasoning by stating that pharmacokinetics is the study of what the body does to a compound, which includes, among other things, uptake. Given that Crooke states that we can't predict in vivo pharmacokinetics from in vitro uptake studies, and since by applicants' admission, uptake is a a part of pharmacokinetic profile, according to this passage, it follows that simply because an oligo is taken up in vitro, we have no idea whether it will be taken up in vivo, regardless of the degree of target inhibition. Applicants thus appear to contradict their own arguments. At the least, applicants have failed to clearly indicate where the mischaracterization occurs. Significantly, applicants have not presented any arguments at all regarding the three other review paper cited in the previous Office action in support of applicants lack of enablement.

Applicants indicate that the absence of working models does not preclude the enablement of their invention, and that the enablement requirement is different from the considerations made by the FDA for drug approval. Applicant is reminded that no such requirements have ever been made, nor is one being made now. Applicants further argue that the fact that there are relatively few successful examples of antisense inhibition in vivo is not evidence of lack of enablement. Applicants state that "the absence of a positive result is not evidence of a negative result". In response, applicant should be aware that in order to be enabled, one must be able to reasonably predict, based on the level of guidance provided in the specification and prior art, that over the scope claimed, a positive result will occur without one of skill having to resort to undue experimentation. Applicants reference to the absence of a positive result in the prior art places a heavy burden on the specification to provide adequate enabling disclosure. As has been set forth in previous Office actions, applicants disclosure of the inhibition of a gene in cell culture is not considered to be representative of the complex internal milieu of the whole animal, and therefore not considered an analogous model system. See the five review articles cited in the 35 U.S.C. § 112 1st paragraph enablement rejection in the Office action mailed February 7, 2003.

The remainder of applicants' arguments regarding the rejection for lack of enablement are drawn to exhibits submitted after final. Applicant has not indicated any reason why these references were not submitted during the prosecution of this application, and accordingly, these exhibits have not been considered.

Finally, applicants arguments that the claims rejected under 35 U.S.C. § 103(a) as being obvious have been addressed previously. Briefly, the references Koesters et al., Taylor et al., Baracchini et al., and Milner et al. combine to teach all the elements of applicants invention. Applicant argues that each reference, when looked at individually, does not teach the claimed invention. However, the claims have not been rejected under 35 U.S.C. § 102, but rather under 35 U.S.C. § 103(a). Thus, the proper test is not whether each reference teaches the invention individually, but rather whether what their combined teaching would have suggested to one of ordinary skill in the art at the time the invention was filed. Contrary to applicants' assertion, motivation to combine the references was set forth in the Office action dated May 7, 2002, and is provided both by Koesters et al., who teaches that the claimed target is upregulated in specific tumor cells, making it an attractive candidate for inhibition, and by Taylor et al. who teach that antisense inhibition is a preferred mechanism for studying the function of genes, and that antisense molecules can be generated against any target of known sequence. Finally, Taylor et al. provide a reasonable expectation of success by stating that with modern software screeing programs and high-affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%. For these reasons the instant rejection of record is maintained.

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600